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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,959	12/15/2003	Karin Drechsel	1/1156-1-C1	3400

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EXAMINER	
HAGHIGHATIAN, MINA	

ART UNIT	PAPER NUMBER
1616	

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10/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,959	DRECHSEL ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-31 and 38-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20, 22-31, 38-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the response filed on 08/15/07. No claims has been amended, cancelled or newly added. Accordingly, claims **1-20, 22-31 and 38-95** remain pending.

Applicant's arguments regarding provisional Double Patenting rejections are persuasive. However, upon further considerations claims are considered obvious over Freund and Jager references, as explained below. Since claims are not in condition for allowance at this time the Double Patenting rejections over the cited Applications remain active.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-20, 22-31, 50, 53-80 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al (DE 19653969 as evidenced by US 2001/0008632).

Freund teach pharmaceutical preparations in the form of **aqueous solutions** for the production of propellant-free aerosols for inhalation for the therapy of obstructive lung diseases. Pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution or a **solvent mixture of ethanol and water**. The amount of dissolved

pharmaceutical in the preparation is **between 0.001 and 30%,** and preferably between 0.05 and 3%. All substances which are suitable for application by inhalation and which are soluble in the specified solvent can be used as pharmaceuticals in the new preparation. Of especial interest are betamimetics, anticholinergics, antiallergic, antihistamines and steroids, as well as combinations of these active ingredients (sections [0001] to [0007]).

Freund teaches that addition of an effective amount of a complexing agent, such as, EDTA, citric acid, ascorbic acid and their salts, and more especially disodium salt of ethylenediaminetetraacetic acid, eradicates the problem of spray anomalies. The effective quantity of complexing agent Na-EDTA is between 10 and 100 mg/100 ml. Also if necessary, ethanol can be added to increase solubility up to 70% by volume. Other adjuvants such as preservatives, especially benzalkonium chloride can be added in amounts of between 8 and 12 mg/100 ml (sections [0009] to [0013]).

Freund discloses a list of compounds which can be used as active ingredients, singly or in combination, in the aqueous pharmaceutical preparation. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility. The list includes; **tiotropium bromide**, budesonide, beclomethasone, disodium cromoglycate, etc. The solutions are set to a pH of 3.2 to 3.4 with 0.1 or 1 N **HCL** in 100 ml of finished preparation (see sections [0014] to [0046] and [0055]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations comprising tiotropium, solvent, an acid and other additives such as benzalkonium chloride with a pH level of 3.2 to 3.4 as taught by Freund et al to prepare the same formulations with a pH of less than 3.2 or 2.0 to 3.0 with a reasonable expectation of successfully preparing safe and stable formulations. In another word, the claims would have been obvious because the technique for improving a particular product was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. In this situation the improvement is lowering pH levels. One of ordinary skill is well aware that by adjusting the concentration of the acid the pH levels would be adjusted. Freund et al teach that low pH levels are suitable for the said formulations, and one could further lower the pH levels to test for stability.

Claims 1-20, 22-30, 50, 53-80 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bozung et al (DE 19921693 as evidenced by US patent 6,433,027).

Bozung et al teach medicament compositions based on anticholinergic compounds which have a long-lasting effect and betamimetics, which have a long-lasting effect, processes for their production and their use in the therapy of respiratory ailments, especially **COPD** (col. 1, lines 11-16). **Tiotropium bromide monohydrate** is the preferred anticholinergic (col. 5, lines 51-55). The medicaments for inhalation are

dissolved in an **aqueous or ethanolic solution**, wherein solvent mixtures of ethanol and water are also suitable. Other adjuvants, such as preservatives, e.g. benzalkonium chloride in concentration range of 8 to 12 mg/100 ml are added. Complex formers like EDTA, **citric acid, ascorbic acid** can be added. The formulations have a pH of 3.4 and the medicament is present in an amount of **0.001 to 5%** (see col. 6, line 39 to col. 7, lines 17-40).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations comprising tiotropium, solvent, an acid and other additives such as benzalkonium chloride with a pH level of 3.4 as taught by Bozung et al to prepare the same formulations with a pH of less than 3.2 or 2.0 to 3.0 with a reasonable expectation of successfully preparing safe and stable formulations. In another word, the claims would have been obvious because the technique for improving a particular product was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. In this situation the improvement is lowering pH levels. One of ordinary skill is well aware that by adjusting the concentration of the acid the pH levels would be adjusted. Bozung et al teach that low pH levels are suitable, and one could further lower the pH levels to test for stability.

Claims 1-18, 20, 22-26, 28-31, 50, 53-69, 71-76, 78-80 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jager et al (WO 9413262).

Jager et al teach stabilized medicinal aerosol solution formulations comprising medicaments that degrade or decompose by interaction with solvents or water. The most preferred examples of the medicaments for use in the aerosol solution formulations include ipratropium bromide, **tiotropium bromide** and fenoterol hydrobromide (see page 8, lines 3-9). Suitable solvents include ethanol and water (see pages 9-10 and examples). One or more acids are added to effect the rate of degradation of the medicament and adjust the pH. Such acids include hydrochloric acid and citric acid. In aqueous solution the rate of hydrolysis and esterification is typically pH dependent. In aqueous solution, the degradation of ipratropium bromide exhibits a pH-rate minimum at pH 3.5. Acid equivalent is given in units of normality which defines a **pH range** equivalent to **2.0-4.7** in an aqueous system (see pages 10-12).

Although, Bozung et al do not exemplify a formulation comprising tiotropium bromide, a solvent and an acid, where the formulation ahs a pH range of 2.0-3.0, the reference provides sufficient disclosure to one of ordinary skill in the art to make and use the formulations as claimed. Specifically, Bozung discloses stabilized formulations comprising an active agents such as tiotropium bromide and a solvent and teaches adding one or more acids to adjust the pH to a range of 2.0-4.7. It is also clearly taught that the stability or rate of decomposition of the said formulations are pH dependent. Thus the claims would have been obvious because a person of ordinary skill in the art would have been motivated to prepare the formulations according to the teachings of Jager et al to achieve the claimed invention and that there would have been a reasonable expectation of success.

Claims 38-49, 51, 52, 81-92, 94 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al or alternatively over Jager et al as applied to claims listed above, and further in view of Weston et al (WO 9114468).

Freund et al, discussed above, lacks specific teachings on the inhalation device.

Weston et al discloses a metered dose inhaler which incorporates metering means for metering a quantity of fluid, and the atomizing means is provided by a mechanical break up device through which the metered quantity of fluid is passed to atomise it when it is subject to said increase in pressure (page 7, lines 5-9). For dispensing a spray of an aqueous solution of a medicament for inhalation into lungs, the droplet size is desirably less than 10 micrometers, typically 2 to 6 micrometers.

Weston also discloses that very high pressures can be generated in the pump cylinder or pressure and nozzle orifice diameters can be used, for example up to 100 micrometers, typically greater than 30 to 50 micrometers. The preferred pressures are from 50 to 400 bar, and more preferably from 100 to 350 bar with nozzle orifice of from 1 to 12 micrometers (page 12, lines 1-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have utilized the preparation of Freund et al by incorporating it in a device suitable for such preparations and because it is made simpler in design and cheaper to produce and suited to its function, as taught by Weston et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-20, 22-31 and 38-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/068,134 (US 20050147564). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent comprising a tiotropium salt in a concentration range of between 0.0005% and 5% by weight, a steroid, a solvent such as water or ethanol and a preservative, wherein the

formulation has a pH of from 2.0 to 3.5. The claims of instant application are drawn to a similar preparation. The difference is that the steroid is not required.

This is a provisional obviousness-type double patenting rejection.

Claims **1-20, 22-31 and 38-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/392,558 (US 20040019073). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a tiotropium salt in a concentration range of between 0.01 and 0.06 g per 100 ml of formulation, a solvent such as water and a preservative, wherein the formulation has a pH of from 2.7 to 3.1. The claims of instant application are drawn to a similar preparation. The difference is that the concentration range of tiotropium is slightly different.

This is a provisional obviousness-type double patenting rejection.

Claims **1-20, 22-31 and 38-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/267,354 (US 20060057074). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the co-pending application are drawn to a formulation comprising a first active agent

comprising a tiotropium salt, a steroid, a betamimetic and a solvent such as water or ethanol. The preparation has a pH of from 2.0 to 7.0 (claim 17). The claims of instant application are drawn to a similar preparation. The difference is that the steroid and the betamimetic are not required.

This is a provisional obviousness-type double patenting rejection.

Claims **1-20, 22-31 and 38-95** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/006,940 (US 20050148562). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. Instant claims are drawn to formulations comprising an anticholinergic, preferably tiotropium and a second active agent such as a steroid. Formulations can be in a solution form and thus require a solvent. The preferred pH rang is from 2 to 7 (see e.g. claims 114 and 229). The claims of instant application are drawn to a similar preparation. The difference is that the second active agent such as steroid is not required.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments, filed 08/15/07, with respect to Provisional Obviousness Double Patenting rejections have been fully considered and are persuasive. However, upon reconsideration new grounds of rejections are being applied and since the claims

are not in condition for allowance at this time the said Double Patenting rejections remain pending.

Furthermore, it should be noted that the arguments of 11/07/05 regarding unexpected activity were reviewed and reconsidered and found unpersuasive and also not commensurate with the scope most claims. The data provided are from four formulations each comprising tiotropium bromide. The independent claims and many of the depending claims are drawn to tiotropium or a salt thereof. It is known in the art that different salts behave differently. Applicant has not shown what the stabilizing pH would be for other salts of tiotropim than bromide. The arguments regarding unexpected activity are not persuasive because all formulations show some degradation and simple improvement of one over other (e.g. pH of 3.0 over 3.2) is not support for patentability and is not distinguished.

It is noted that co-pending Application 10/730,796 has been abandoned since last office Action and is no longer included in Provisional Double Patenting rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mina Haghighatian
Patent Examiner
October 19, 2007